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Letter to the Editor

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Rise and fall of 17 alfa-hydroxyprogesteronecaproate

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Dear Editor;

Low progesterone levels during early pregnancy is one of the factors that is related with threatened abortion. 17 alpha-hydroxyprogesterone caproate (17-OHPC), a synthetic progestogen, was first approved in 1956 to treat a variety of gynecological and obstetric conditions in pregnant women, including threatened abortion and preterm birth. 17-OHPC is a selective progesterone receptor agonist and is prepared for intramuscular (im) use in oil solution. 17-OHPC is licensed under the brand name Delalutin in USA and Proluton in Europe. High-dose (250 mg/mL intramuscular load) 17-OHPC was widely prescribed to pregnant women in the USA and Europe in the 1950s and 1960s. In October 1973, the U.S. Food and Drug Administration (FDA) reported the lack of significant evidence for the use of 17-OHPC for threatened abortion prevention and raised concern about the association of 17-OHPC with fetal congenital heart defects.[1] Then, all pregnancy-related indications were removed from the label, citing the possibility of teratogenic effects associated with systemic use and 17-OHPC was marked as Category D in pregnant women in 2009 by FDA.[1]

As a part of the Accelerated Approval Program, the FDA reapproved 17-OHPC in February 2011 under the name Makena for pregnant women with a history of spontaneous preterm birth, based on a randomized trial by Meis et al.[2] published in 2003. Meis et al showed a reduction in the incidence of preterm birth at 37 weeks. Use of IM 17-OHPC 250 mg weekly between 16/20 weeks to 36 weeks is recommended by the guidelines for prevention of preterm birth in women with a previous history of preterm birth. In 2009, detailed analysis of the Meis study by Calda[3] noted a statistically insignificant increase in fetal deaths and stillbirths among women using 17-OHPC. In 2007 Rouse[4] reported no improvement in the reduction of preterm births in twin pregnancies with the use of 17-OHPC. Similarly, Combs[5] reported no improvement in preterm delivery and neonatal delivery in twins and triplets with the use of 17-OHPC. Embryo-fetal toxicity related with 17-OHPC were demonstrated in two experimental studies on rhesus monkeys and rodents.[6] Maternal effects of 17-OHPC came under spotlight. two studies reported a higher incidence of abnormal glucose testing and gestational diabetes in women receiving 250mg 17-OHPC weekly while one study reported no increased risk.[7,8]

As a part of accelerated approval of 17-OHPC, FDA needed a confirmatory trial. A multi-center, randomized, double-blind, vehicle-controlled clinical trial (PROLONG Trial) was conducted on women with singleton pregnancies who had a history of spontaneous preterm delivery during their previous pregnancies. PROLONG Trial failed to show any reduction in preterm delivery before 35 weeks and neonatal morbidity and mortality.[9] As a result FDA approal of Makena was withdrawn.[9]

Although the drug is drawn form the market the questions about fetal long term effects are still in the spotlight. A recent publication by Murphy et al.[1] published in 2020 raised concern about the possible link between inutero 17-OHPC exposure and cancer risk in the offspring.[1] After analyzing mother-child records who took antenatal care at e between 1959 and 1966 and the Cancer registry, out of 18,751 offsprings 1% (n=234) were found to be exposed to 17-OHPC in-utero mostly during the first trimester due to threatened abortion. The median follow-up period was 45.9 years. Among the exposed 234 offsprings, 23 were diagnosed with cancer. Two of the cancer cases were diagnosed during childhood (age <18 years) and 21 in adulthood (age ≥18 years). As a result, compared to the offsprings not exposed to 17-OHPC, offsprings exposed had an increased risk of any cancer (adjusted Hazards Ratio: 1.99, 95% CI 1.31, 3.02). Exposure in the first trimester was associated with an increased risk of cancer (adjusted hazard ratio, 2.57; 95% confidence interval, 1.59e4.15), and the risk increased with the number of injections (1e2 injections: adjusted hazard ratio, 1.80; 95% confidence interval, 1.12e2.90; 3 injections: adjusted hazard ratio, 3.07; 95% confidence interval, 1.34e7.05). Late

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exposure in the second or third trimester increases the risk in male (adjusted hazard ratio, 2.59; 95% confidence interval, 1.07e6.28) but not for the female (adjusted hazard ratio, 0.30; 95% confidence interval, 0.04e1.11) offspring. The risk of colorectal, prostate, and pediatric brain cancer was higher in the offspring exposed to 17-OHPC in the first trimester than the offspring not exposed. Most of the patients evaluated were born in the 1960s and the preparation was just being used and many pregnant women received repeated high-dose treatment. This study demonstrated that exposure to 3 or more injections, especially in the first trimester of pregnancy, increased the risk malignancy and late exposure increased the risk of the male gender.

The limitations of the Murphy et al.[1] is its retrospective design and the limited number of the analyzed cases and confounding factors. Prospective studies that will clarify the precise mechanisms contributing to cancer risk would probably take years. However, in the meantime, these findings raise significant concern regarding the use of 17-OHPC during pregnancy. New progesterone formulations such as vaginal progesterone are compared to 17-OHPC and show more favourable results.[10] However further studies with new formulations and different routes of delivery are requirred for an evidence-based recommendation for prevention of preterm delivery when different formulations are concerned.

ETHICAL DECLARATIONS

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Referee Evaluation Process: Externally peer-reviewed

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